C2 Sub D7

the group consisting of SEQ ID NOS:1-5 and wherein the mosaic polypeptide is not the HCV polyprotein.

REMARKS

Claims 1-31 were pending in this application. Claims 1-6 and 14-25 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 7-13 and 26-31 were under examination. New claims 32-~~39~~ 40 are added by the present amendment. Attached hereto is "Version with markings to show changes made" which shows the changes made to already pending claims by the current amendment. No new matter is believed added.

Support for amendment of claims 9-13 can be found in the claims as previously pending and in the claim 7 from which they depended. Support for new claims 32-40 can be found on page 2, line 22 to page 3, line 6 and elsewhere throughout the specification as filed.

In light of the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Objections to New Matter under 35 U.S.C. § 132

Amended claim 7 is objected to because it allegedly introduces new matter into the disclosure. The added material, which is allegedly not supported by the original disclosure is stated to be, "wherein at least two antigenic epitopes are from the same region of variants of the same protein."

Applicants traverse Examiner's objection to the amendment, but submit that the objection is moot in light of cancellation of claim 7 as directed herein.

Applicants request removal of this basis of objection.

II. Rejections under 35 U.S.C.§ 112, second paragraph

Claims 7 and 26 remain rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner reasserts the earlier basis for the rejection.

Claims 7 and 26 were rejected under 35 U.S.C. § 112, second paragraph, for being indefinite and for not distinctly claiming the subject matter of the invention. The basis for this rejection, as stated in the Office Action of December 26, 2001, was that the "metes and bounds of 'one or more antigen' epitopes [we]re not defined." The Examiner then further stated, correctly, that the limitations from the specification are not to be read into the claims, citing *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, the Examiner then stated that because there are many antigen epitopes found within the regions recited in the claims, the claims should recite specific epitopes. Finally, the Examiner stated that because "comprising" is "open language, which fails to define any precise amino acid sequence structure...[t]he claims should use more defined language to describe ...amino acid sequence..."

In light of the cancellation of claims 7 and 26, Applicants submit that the currently pending claims each use more defined language that fulfills the apparent standard requested by the Examiner as was reflected in reference to *In re Van Geuns*. Nevertheless, Applicants maintain that even though the presently pending claims do comply with the apparent standard put

forth by the Examiner earlier, compliance with the alleged standard is not required for patentability.

III. Rejections under 35 U.S.C.§ 102

A. Claim 7 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chien et al. (a) (PNAS USA (1992)). Specifically, Chien et al. teaches a fusion protein comprising a sequence that includes sequence from the nucleocapsid protein C, NS3 protein, and NS4 protein. Applicants' earlier arguments that Chien et al. (a) does not anticipate the claims as amended to require at least two antigenic epitopes from the same region of variants of the same protein has been rejected because the Examiner alleges there is not support for the amendment of the claim. Specifically, the Examiner states that the disclosure of page 2, lines 21-29 teaches only that epitopes that constitute the claimed mosaic peptide are selected from the disclosed SEQ ID NO:1-5...," that these sequences are "...all from HCV genotype 1b..." and that there is no indication that the epitopes of claimed mosaic peptide of HCV are selected and reconstructed from different species of the HCV family" (emphasis added).

In light of the cancellation of claim 7, Applicants submit that this basis of rejection is moot and request allowance of further pending claims to issue.

B. Claims 7 and 8 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chien et al.(b) (J. Gastro. Hepato. 1993, Vol. 8, pp. S33-39). Specifically, it is alleged that Chien et al. teach a general method for using recombinant antigen polypeptide antigen (C25) comprising six proteins representing the structural regions of core, the envelope and non-structural regions (C33C) and NS3-NS4 (C11-3) and NS5 to detect the anti-HCV antibody. The general method, using the combined antigens was deemed superior to using the single peptide assay.

Furthermore, the Examiner states that the Applicants' previous argument has been considered, but has not been found persuasive because the Applicants fail to provide the support of the amendment of claim 7 as described *supra*.

Furthermore, the Examiner contends that "the six protein polypeptide disclosed by Chien et al. (b) comprises the structural regions of core, the envelope and nonstructural regions and NS3-NS4 (C11-3) and NS5." On the basis of this understanding, it is alleged to anticipate the claims 7, 8 and 26. The Examiner also alleges that the seventh protein only contains non-structural regions NS3 and NS3-NS4 and, consequently, only anticipates claim 7.

In light of the cancellation of claims 7-8, Applicants submit that this basis of rejection is moot and request allowance of further pending claims to issue.

IV. Rejection under 35 U.S.C. § 103

A. Claims 7, and 9-12 and 26-31 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chien et al. (a) and Kato et al. Specifically, it is alleged that Chien et al., which teach a fusion protein comprising the sequence structures of certain NS3 fragments, NS4 fragments and nucleocapsid protein C (core) fragments, render the present invention obvious. Applicants' previous Response has been characterized by the Examiner as on one hand arguing that the sequences cited in the reference are not adequate to disclose the sequences as disclosed in the claims, while on the other hand arguing that the characterization of the present invention as being a particular sequence is too narrow.

In response, Applicants first note that claims 7-8 and 26-31 have been cancelled. Accordingly, Applicants submit the following response to the noted rejection to the degree it

applies to still pending claims 9-13 as amended. Specifically, the present invention as claimed recites sequence from particularly defined fragments of the HCV polyprotein. Thus, the present invention as claimed is a mosaic polypeptide comprising one or more epitopes from the HCV core, NS3 and/or NS4 proteins, wherein the core protein amino acid sequence included is amino acid residues 1-91, that for NS3 protein are residues 1471-1573 and/or 1789-1867, and that for NS4 are 1789-1867 and/or 1916-1948. As previously acknowledged by the Examiner, these particular sequences do differ from those used by Chien et al. Nonetheless, the Examiner asserts that the claimed structures of HCV, including those recited in claims 9-13, are known in the art as evidenced by Kato et al. who disclose all the claimed sequences from claims 7 and 9-12 with 100% homology. In particular, it is alleged by the Examiner that it would have been obvious to one of ordinary skill in the art at the time the invention was filed to be motivated by the reference of Chien et al. (a) and further in view of the sequences disclosed by Kato et al. to make a mosaic polypeptide comprising HCV core, NS3 and NS4 for detecting anti-HCV antibodies with improved sensitivity. Hence, it is concluded by the Examiner that the claimed invention as a whole is *prima facie* obvious absent unexpected results. Applicants respectfully disagree as the claimed mosaic polypeptide of the invention requires inclusion of particular sequences, namely, those corresponding to amino acid residues 1-91, 1471-1573, 1789-1867, 1789-1867 and/or 1916-1948 of the HCV polyprotein, wherein the mosaic polypeptide is not the HCV polyprotein. Importantly, the combination of Chien et al. (a) and Kato et al. do not provide these particular limitations of sequence. As a result, Chien et al. (a) and Kato et al. can not properly establish a *prima facie* case of obviousness for this invention. Specifically, they do not fulfill the three criteria that must be met for a *prima facie* case of obviousness to be established, namely, (1) some suggestion or motivation to combine reference teachings; (2) a reasonable expectation of success; and (3) the combination of references must teach or suggest all claim limitations.

As it relates to the first criterion, there is no teaching in either Chien et al. (a) or in Kato et al. that the assay of Chien et al. is deficient or requires further sequence. Correspondingly, there can be no motivation to combine Kato et al. with Chien et al. Furthermore, even if there was a teaching that Chien et al. was deficient, without further teaching or guidance as to making the combination with Kato et al., a rejection based upon a finding of *prima facie* obviousness is improper. The PTO can satisfy its burden of establishing a prima facie case of obviousness "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, U.S.P.Q.2d 1596 (Fed. Cir. 1988). Thus, the first required criterion is not met.

Rather, there is only an unsupported conclusion *on the part of the Examiner* that making a "mosaic polypeptide comprising HCV core, NS3, NS4 and NS5" polypeptide would result in improvements in the art. As such, this statement is clearly not a recitation of any motivation or suggestion *within the teachings of the art* to combine the cited references. The cited publications do not reach this conclusion nor suggest it. The Examiner's conclusion, in fact, is only a cautionary example of the hindsight-based obviousness analysis against which the proper standards of determining obviousness have been developed to guard against and against which the courts warn. "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998).

Furthermore, in respect to the third criterion, Applicants submit that the present claims directed to regions of HCV polyprotein sequence defined with particularity cannot be rendered

obvious by a reference disclosing the complete HCV polyprotein sequence and a reference indicating that certain other smaller regions from that sequence can be used. In particular, it is well-recognized in the patent law that a claimed nucleic acid or amino acid is not obvious unless the cited art provides the motivation and specific guidance to obtain the claim molecule (*In re Bell* (26 U.S.P.Q. 2d, 1529-1532 (Fed. Cir.1993)). Thus, even if one were to accept the proposition that Chien et al. (a) provides a general motivation to make a mosaic polypeptide peptide and Kato et al. provides the complete sequence of the HCV polyprotein, it is absolutely clear that this combination does not provide any guidance that points to particular mosaic polypeptides as presently claimed.

As is discussed in *In re Bell* (26 U.S.P.Q. 2d, 1529-1532 (Fed. Cir.1993), the sequence of a nucleic acid encoding a specific amino acid was not obvious despite the disclosure in the prior art of the amino acid sequence encoded by the claimed nucleic acid, and the unquestioned teaching in the art of how to identify each and every nucleic acid that could encode the protein. The rationale for this decision was that a claimed molecule is not obvious unless the art points to that molecule. It is not enough that the art would allow the skilled person to find the claimed molecule. This, Applicants submit, is analogous to the present case and, accordingly, the presently claimed mosaic polypeptides are not obvious over the cited art. It is, further, analogous to an earlier application, 08/921,887 (now issued U.S. patent No. 6,030,771), wherein the Examiner found claims drawn to mosaic proteins that recited particularly defined sequences, i.e., some subset of SEQ ID NOS:23-33, drawn from HCV polyprotein sequence patentable. While the sequences defined as SEQ ID NOS:23-33 in the '771 patent are not the same as claimed herein, Applicants submit that there is no basis for distinction on those grounds from the present case wherein a different subset of sequences are used to define new and unobvious mosaic polypeptides. Specifically, the particular regions of sequence required to be present in the

mosaic polypeptides of the present invention differ from any of those sequences included or described in the prior and the prior art does not teach the particular sequences claimed any more than would the knowledge of HCV polyprotein sequence render a mosaic polypeptide comprising particular sequences obvious and unpatentable; which, of course, it does not as was evidenced by patentability of claims directed to polypeptides comprising SEQ ID NOS:23-33 in the '771 patent. Thus, Applicants submit that it should be clear that the third criterion is also not met by the present combination of references.

Finally, as it relates to the second criterion, Applicants submit that in order for there to be a reasonable expectation of success, there must at least be a suggestion or motivation to provide a combination of elements that provides the present invention (i.e., the first criterion must be fulfilled). Indeed, without any such motivation or suggestion, there can be not only no reasonable expectation of success, there can be no expectation of success. Similarly, if the references do not provide all limitations required to provide the claimed invention (i.e., the third criterion is not fulfilled), there can also be no proper finding that there is a reasonable expectation of success as necessarily one of skill in the art would not expect to successfully achieve the invention if the art did not teach its limitations. Thus, for both these reasons, the second required criterion is clearly not met. Applicants request removal of this basis of rejection.

B. Similarly, Claims 7-13 and 26-31 are rejected under 35 U.S.C. § 103(a) over Chien et al. (b) and Kato et al. on the same grounds as stated in the previous Office action. Further, the Examiner states that the Applicants' argument has been fully considered but has not been found persuasive. Specifically, because the reference of Chien et al. teach that the alleged fact that the more antigenic epitopes that are used in the assay, the more sensitivity and

specificity of antibodies you are able to get. This is allegedly demonstrated by use of the polypeptide C25 assay, which, the Examiner states, is a multiple antigenic peptide derived from C, NS3, NS4 and NS5 and HCV, that is superior to the single peptide assay of NS4. This, the Examiner alleges, is the motivation that one of ordinary skill in the art would take to use mosaic polypeptides rather than a single polypeptide to get more sensitive and specific detection of HCV antibodies with a high expectation of success.

In response, Applicants first note that claims 7-8 and 26-31 have been cancelled. Accordingly, Applicants submit the following response to the noted rejection to the degree it applies to still pending claims 9-13 as amended. Specifically, the present invention as claimed recites sequence from one or more of the specified regions of sequences not disclosed in any reference and is therefore novel and unobvious for the reasons detailed above in IV.A above.

C. Claims 7-13 and 26-31 are still rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Valenzuela et al. and in further view of Chien et al.(b) and Kato et al. Specifically, Valenzuela et al. teach a multiple epitope sequence having the general structural formula (I): (A)x-(B)y-(C)z, wherein the (I) is a linear amino acid sequence and the A. B. and C, are epitopes from regions of the HCV polyprotein (e.g., NS3, NS4, and NS5). The Declaration filed on July 18, 2002 under 37 CFR § 1.131 has been considered, but is argued to be ineffective in overcoming the rejection.

In response, Applicants first note that claims 7-8 and 26-31 have been cancelled. Accordingly, Applicants submit the following response to the noted rejection to the degree it applies to still pending claims 9-13 as amended. Specifically, the present invention as claimed recites sequence from one or more of the specified regions of sequences not disclosed in any

reference and is therefore also novel and unobvious for the reasons detailed above in IV.A above.

In regard to claims 33-37 and 39, dependent from independent claims to which each of the above remarks apply, the Applicants refer the Examiner to the MPEP § 2143.03, 1st paragraph, wherein it states, "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)." Accordingly, so as to not unduly burden the Examiner, the Applicants will refrain from presenting additional arguments and support for the nonobviousness of the various dependent claims at the present time, except to note that each of claims 33, 35, 37 and 39 recite specific sequence selected from SEQ ID NOS:1-5, as does independent claim 40. Although by refraining from presenting extensive arguments and support for the nonobviousness of the above-indicated claims, the Applicants do not accede that there is not further basis for establishing the nonobviousness of the dependent claims above and beyond what has already been presented. Therefore, the Applicants reserve the right to establish the nonobviousness of each and every dependent claim in future remarks or comments.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Credit Card Payment Form PTO-2038 authorizing payment in the amount of $614 ($504 for 6 new independent claims and $110 for one month extension of time) is enclosed. This

amount is believed to be correct; however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No.14-0629.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — Date: 1-21-03

Version with markings to show changes made

In the claims:

9. (Twice amended) A [The] mosaic polypeptide comprising an isolated [of Claim 7, wherein the] antigenic epitope of HCV [the] core protein comprising [comprises] amino acid residues 1-91 of the HCV polyprotein, wherein the mosaic polypeptide is not the HCV polyprotein.

10. (Twice amended) A [The] mosaic polypeptide comprising an isolated [of Claim 7, wherein the] antigenic epitope of HCV [the] NS3 protein comprising [comprises] amino acid residues 1471-1573 of the HCV polyprotein, wherein the mosaic polypeptide is not the HCV polyprotein.

11. (Twice amended) A [The] mosaic polypeptide comprising an isolated [of Claim 7, wherein the] antigenic epitope of HCV [the] NS4 protein comprising [comprises] amino acid residues 1789-1867 of the HCV polyprotein, wherein the mosaic polypeptide is not the HCV polyprotein.

12. (Twice amended) A [The] mosaic polypeptide [of Claim 7, further] comprising an isolated [a second] antigenic epitope of HCV [the] NS4 protein comprising [, wherein the second antigenic epitope comprises] amino acid residues 1916-1948 of the HCV polyprotein, wherein the mosaic polypeptide is not the HCV polyprotein.

13. (Thrice amended) A [The] mosaic polypeptide comprising an isolated [of claim 8, wherein the] antigenic epitope of HCV [the] NS5a protein comprising [comprises] amino acid residues 2322-2423 of the HCV polyprotein, wherein the mosaic polypeptide is not the HCV polyprotein.